Complete Summary

GUIDELINE TITLE

The role of erythropoietin in the management of cancer patients with non-hematologic malignancies receiving chemotherapy.

BIBLIOGRAPHIC SOURCE(S)

Systemic Treatment Disease Site Group. Quirt I, Bramwell V, Charette M, Oliver T. The role of erythropoietin in the management of cancer patients with non-hematologic malignancies receiving chemotherapy [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2005 Mar [online update]. 25 p. (Practice guideline report; no. 12-1). [71 references]

GUIDELINE STATUS

This is the current release of the guideline.

The FULL REPORT, initially the full original Guideline or Evidence Summary, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

- Non-hematologic cancer
- Anemia (directly or indirectly related to malignancy)

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Prevention
Treatment

CLINICAL SPECIALTY

Internal Medicine
Oncology
Radiation Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To make recommendations regarding the use of erythropoietin (EPO) to reduce the need for transfusion of red blood cells in patients with non-hematologic malignancies receiving chemotherapy
- To evaluate whether the administration of erythropoietin improves the quality of life of individuals receiving chemotherapy for the treatment of cancer

TARGET POPULATION

These recommendations apply to cancer patients with non-hematologic malignancies receiving chemotherapy who meet the following criteria:

Hemoglobin levels $\leq$100 g/L during the initial courses of myelosuppressive cancer chemotherapy

OR

Hemoglobin levels $\leq$120 g/L with symptoms of anemia affecting functional capacity/quality of life

AND

Anemia directly or indirectly related to malignancy, but not caused by hemolysis, gastrointestinal bleeding, and iron or folate deficiencies

INTERVENTIONS AND PRACTICES CONSIDERED

Administration of erythropoietin during chemotherapy

MAJOR OUTCOMES CONSIDERED

- First transfusion requirement from the start of chemotherapeutic medication is the main outcome of interest.

- Hemoglobin levels
- Quality of life, adverse events, and costs are also considered.

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

March 2003 Guideline

The medical literature was searched using the MEDLINE (Ovid) (1966 through January 2003), CANCERLIT (Ovid) (1983 through October 2002), and Cochrane Library (Issue 4, 2002) databases. In addition, the Physician Data Query clinical trials database and abstracts published in the conference proceedings from the meeting of the American Society of Clinical Oncology (1997-2002) were searched for reports of new or ongoing trials. The Canadian Medical Association Infobase and the National Guideline Clearinghouse databases were searched for related clinical practice guidelines. Reference lists from relevant articles and reviews were searched for additional trials.

The literature search combined disease specific terms (neoplasms/ or cancer:.tw. or malignan:.tw. or tumour:.tw.) with treatment specific terms (erythropoietin/ or erythropoietin.mp. or epo.tw. or epoetin.tw. and drug therapy/ or chemotherapy.tw.) with search specific terms for the following study designs: practice guidelines, systematic reviews or meta-analyses, reviews, randomized controlled trials, controlled clinical trials, and economic evaluations.

An additional search was performed using MEDLINE, CANCERLIT, and the Cochrane Library for the same years to locate reports of non-randomized trials evaluating the quality of life of cancer patients receiving erythropoietin. The search terms for erythropoietin described above were combined with "quality of life" (MeSH and text word) or "qol". In addition, the 1998–2002 proceedings of the annual meetings of American Society of Clinical Oncology were also searched for reports of newly completed trials.

March 2005 Update

The medical literature was searched using the MEDLINE (Ovid) (2003 through March 2005), EMBASE (Ovid) (2003 through March 2005), and Cochrane Library (Issue 1, 2005) databases. In addition, the Physician Data Query clinical trials database and abstracts published in the conference proceedings from the meeting of the American Society of Clinical Oncology (2003–2004) and the European Society of Clinical Oncology (2004) were searched for reports of new or ongoing trials. The Canadian Medical Association Infobase and the National Guideline Clearinghouse databases were searched for related clinical practice guidelines.

Reference lists from relevant articles and reviews were searched for additional trials.

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they were fully published reports or published abstracts and met the following criteria:

- Randomized controlled trials that compared erythropoietin (EPO) with placebo or observation
- Specified outcome measures that could be analysed included the number of patients transfused during the period of follow-up, quality of life, change in hemoglobin, and adverse effects of EPO
- Subjects were patients with cancer receiving chemotherapy
- Non-randomized reports of cancer patients receiving EPO were considered if they reported on quality of life outcomes.

Exclusion Criteria

Articles were excluded from the systematic review of the evidence if they were:

- Trials published in a language other than English
- Trials involving only patients with hematologic malignancies originating in the bone marrow
- Trials involving patients receiving radiotherapy or chemoradiotherapy

NUMBER OF SOURCE DOCUMENTS

March 2003 Guideline

24 randomized controlled trials, 10 non-controlled trials, 1 meta-analysis, and 2 clinical practice guidelines were reviewed.

March 2005 Update

14 additional randomized controlled trials, 1 meta-analysis, and 1 clinical practice guideline were identified and included in the practice guideline report.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Randomized Controlled Trials
Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

The number of patients transfused during the period of follow-up reported across the randomized trials was combined to obtain a more precise estimate of the treatment effect of erythropoietin (EPO) in order to determine the clinical significance of the results. Combining results across trials provides added power for detecting the efficacy of the treatment and improves the reliability or confidence of the point estimate. Results were pooled using the software package Metaview© Update Software. The overall effect of EPO is expressed as a risk ratio (RR) with a 95% confidence interval (CI) and the percent relative risk reduction (RRR). The risk ratio is the ratio of the risk of target events in treated patients to the risk of target events in control patients. Target events were unfavourable (e.g., transfusion required), so that estimates less than 1.0 favoured EPO, and estimates greater than 1.0 favoured control (no EPO or placebo). The relative risk reduction compares the risk of target events in the treatment group with the risk of target events in the control group [RRR = 1 - RR x 100]. Because of suspected statistical heterogeneity across studies related to methodological quality, EPO dose, hematologic status, tumour type of patients at trial entry, or chemotherapy regimen, a random effects model was used. Sensitivity analyses were done to determine whether particular study characteristics might have an effect on the estimate of treatment effect. Five study characteristics were identified as potentially important: the use of a placebo control, a study population including patients with documented anemia at the start of the trial, a study population including patients with normal hemoglobin levels at the start of the trial, platinum-based chemotherapy regimens, and non-platinum based chemotherapy regimens.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Two issues were noted and discussed by members of the Systemic Treatment Disease Site Group (DSG). The first was that the recommendation did not address when erythropoietin (EPO) should be started: should EPO be administered at the beginning of chemotherapy or later? Because the randomized evidence did not address the administration of EPO in a consistent way, it was agreed to assign the responsibility for determining the optimum time to start EPO to clinical judgement. The second issue centred on making a recommendation about the use of EPO in patients receiving non-platinum-based chemotherapy. The biological effect of EPO would be the same for platinum- and non-platinum-based chemotherapy; however, the baseline risk for anemia is lower in non-platinum-based chemotherapy. The pooled results suggest that there is a stronger effect for EPO in patients receiving platinum-based chemotherapy than in those receiving non-platinum-based chemotherapy. Members of the Systemic Treatment Disease Site Group felt that although the evidence is stronger for platinum-based

regimens, there is evidence supporting the use of EPO in non-platinum-based regimens and the guideline recommendation should reflect this.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Practitioner feedback was obtained through a mailed survey of 134 medical oncologists in Ontario. The survey consisted of 21 items evaluating the methods, results, and interpretive summary used to inform the draft recommendations outlined and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The results of the survey have been reviewed by the Systemic Treatment Disease Site Group.

The practice guideline report was circulated to 14 members of the Practice Guidelines Coordinating Committee (PGCC) for review and approval. Eleven of the fourteen members of the PGCC returned ballots. All of the eleven PGCC members approved the practice guideline report as written. Two PGCC members requested minor wording changes to improve the clarity around the recommended dose of erythropoietin, and estimated administration cost of erythropoietin. Minor additions to the text were suggested under the sections of Synthesizing the Evidence and Choice of Topic and Rationale.

Based on the comments of the members of the PGCC, the Systemic Treatment Disease Site Group modified the practice guideline report to address the above issues. As a result, minor changes to the text of the practice guideline were made.

The practice guideline reflects the integration of the draft recommendations with feedback obtained from the external review process. It has been approved by the Systemic Treatment Disease Site Group and was approved by the Practice Guidelines Coordinating Committee.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- Erythropoietin is recommended as a safe and effective treatment option if given with the intent of reducing the incidence of symptomatic treatment-related anemia and the need for red blood cell transfusion.
- Erythropoietin is recommended as a reasonable treatment option in patients in whom a slow decline in hemoglobin is associated with increased fatigue and perceived reductions in quality of life.
- Erythropoietin is not recommended in situations where rapid (i.e., less than 4 weeks) recovery of hemoglobin is required.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The guidelines are supported by randomized controlled trials, meta-analyses, and clinical practice guidelines.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Twenty-three randomized controlled trials were available for review. A meta-analysis was performed with 30 of the randomized trials that used a common, clinically relevant outcome measure. When compared with control patients, the meta-analysis showed a relative risk for transfusion patients among erythropoietin (EPO) patients of 0.52 (95% confidence interval, 0.46 to 0.60) translating to a 48% relative reduction in the proportion of patients requiring transfusion ($p<0.00001$).

POTENTIAL HARMS

Hypertension has been noted rarely in erythropoietin (EPO)-treated cancer patients. Randomized controlled trials did not detect a difference in adverse effects in erythropoietin-treated patients versus control over the period of follow-up. Long-term adverse effects are not known.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- Transfusion of red blood cells remains the treatment of choice in patients with rapidly developing symptomatic anemia.
- It is most reasonable to recommend erythropoietin to individuals who have a reasonable chance of experiencing relatively long-term survival or cure as an outcome from their chemotherapy. It is these individuals who have the greatest risk of suffering from the long-term complications of transfusion. Individuals in whom short survival is anticipated are better treated by

transfusion for symptomatic anemia since erythropoietin takes approximately four weeks to start elevating hemoglobin levels.

- Although the evidence supporting the use of erythropoietin is stronger for patients receiving platinum-based therapy, erythropoietin is also effective in patients receiving moderately or severely myelosuppressive regimens that do not contain platinum.
- Several randomized trials have shown statistically significant improvements in several domains of quality of life in patients receiving erythropoietin. The clinical significance of these improvements (often of the order of 20% to 40% increase over baseline) in patients with moderate to severe baseline quality of life impairment (generally approximately equal to 50% of maximum scores) also needs to be considered. A clear linear relationship between fatigue and anemia has not been established.
- The Systemic Treatment Disease Site Group (ST DSG) supports the recommended dose schedule approved for marketing in Canada; 150 IU/kg of erythropoietin delivered subcutaneously three times a week for four weeks, increasing to 300 IU/kg subcutaneously three times a week for four weeks if the hemoglobin level has not risen by 10 g/L or the reticulocyte count has not risen by 40 X 10^9/L. If, after that time, the endpoints have not been achieved, therapy is discontinued. If the hemoglobin is rising by more than 20 g/L per month, the dose should be reduced by approximately 25%. The target hemoglobin is usually 120 g/L. A treatment algorithm to guide the use of erythropoietin is shown in Appendix 1 of the original guideline document.
- It is also reasonable to administer 40,000 IU once weekly, increasing after four weeks to 60,000 IU once weekly for four weeks if the endpoints have not been achieved.
- There is a rare but clinically significant risk of pure red blood cell aplasia with erythropoietin in patients with chronic renal failure.
- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or warranties of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Systemic Treatment Disease Site Group. Quirt I, Bramwell V, Charette M, Oliver T. The role of erythropoietin in the management of cancer patients with non-hematologic malignancies receiving chemotherapy [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2005 Mar [online update]. 25 p. (Practice guideline report; no. 12-1). [71 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1997 Apr 4 (revised 2005 Mar)

GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Practice Guidelines Initiative (PGI) is the main project of the Program in Evidence-based Care (PEBC), a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario, Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Systemic Treatment Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Systemic Treatment Disease Site Group disclosed potential conflict of interest information.

GUIDELINE STATUS

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GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- The role of erythropoietin in the management of cancer patients with non-hematologic malignancies receiving chemotherapy. Summary. Toronto (ON): Cancer Care Ontario (CCO). 1997 Apr 4 (revised 2005 Mar). Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on January 5, 1999. The information was verified by the guideline developer as of February 22, 1999. This summary was updated by ECRI on August 6, 2003. The updated information was verified by the guideline developer on September 2, 2003. This summary was updated by ECRI on June 6, 2005. The updated information was verified by the guideline developer on June 15, 2005.

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